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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,410	03/01/2004	Robert L. Martuza	066683-0198	4953

22428 7590 08/18/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
08/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,410	MARTUZA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18-20 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-20 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 05/14/2008 has been entered. Claims 1-15, 17, and 18-27 are cancelled. Claims 16 and 20 are amended. Claims 16, 18-20 and 28-32 are pending and currently under examination.

This application 10/788,410 file don 03/01/2004 is a DIV of 09/625,509, filed on 07/25/2000, now PAT 6,699,468, which is a DIV of 09/004,511, filed on 01/08/1998, now PAT 6,139,834, which is a CON of 08/478,800, filed on 06/07/1995 ABN, which is a CON of 08/264,581, filed on 06/23/1994, now PAT 5,585,096 (changes are in bold for emphasis). The series of parent applications of instant application listed above is based on the Application Data Sheet filed on 08/06/2007.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Previous rejection of claims 16 and 20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

It was noted that in the art G207 is the name of a specific HSV that contains deletions of both copies of the γ34.5 gene as well as a LacZ insertion in the ICP6

gene, which is the large subunit (ICP6) of ribonucleotide reductase (RR). However, the name G207 does not encompasses a cytokine in the HSV vector as required by claim 16.

Claim 16 has been amended to read as follows: A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) an alteration in the 734.5 gene, wherein the mutation results in a lack of function of the γ34.5 gene product.

Claim 20 has been amended to read as follows: The herpes simplex virus of claim 19, wherein said herpes simplex virus is G207 expressing the cytokine.

2. Claims 16, 18-20, and 28-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendment filed on 05/13/2008.*

Claim 16 recites the limitation "the mutation" in "wherein the mutation results in a lack of function of the γ34.5 gene product". There is insufficient antecedent basis for this limitation in the claim. Claims 18-20, and 28-32 depend from claim 16.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 16, 18-20 and 28-32 **remain** rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein said desired protein is a cytokine and wherein the neurovirulence of said herpes simplex virus is attenuated, and for said virus further comprising at least one further gene alteration in ribonucleotide reductase (RR) gene such that no functional ribonucleotide reductase is made, **does not** reasonably provide enablement for a herpes simplex virus with a genome comprising 1) any alteration in the γ34.5 gene and the ribonucleotide reductase gene other than an alteration that results in a lack of function of each gene product, or 2) for a viral particle exhibiting any effect from the alteration other than attenuation of neurovirulence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant's arguments filed 05/14/2008 have been fully considered and they are not persuasive. Previous rejection

is ***maintained*** for the reasons of record advanced on pages 5-11 of the office action mailed on 02/14/2008.

It is noted that, to reflect claim amendments filed on 05/14/2008, the enabled embodiment "an expressible non-herpes simplex virus nucleotide sequence encoding a desired protein" has been replaced with "an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor" in this scope of enablement.

Applicant's Arguments

Applicant argues that claim 16 has been amended to specify that the mutation in the γ34.5 gene results in a lack of function of the γ34.5 gene product. Applicant indicates that the revision is amply supported (see the published application, e.g., at page 2, paragraph [0019], and at page 6, paragraph [0076]) and comports with the Examiner's recommendation (Office Action, at page 6, last paragraph). Applicant indicates that the specification further discloses construction of HSV vectors and impairment of γ34.5 gene expression (published application, pages 4 and 5). Therefore, Applicant argues that the skilled person is enabled by the specification to make HSV mutants as claimed.

Responses to Applicant's Arguments

As documented in the preceding section of rejection of claims 16, 18-20, and 28-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention, the amendments of claim 16 reciting the limitation "wherein the mutation result in a lack of function of the γ34.5 gene product" lacks antecedent basis (see, 112, 2nd paragraph rejection, above). Accordingly, the amended claim 16 continues to read on any alteration of γ34.5 gene because the claim as written, there is no nexus between the altered γ34.5 gene and the mutation, as recited in amended claim 16. In other words, the amended claim 16 as written does not limit the alteration in the γ34.5 gene to a null mutation of the γ34.5 gene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 16, 28, and 29 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific

promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994). Applicant's arguments filed 05/14/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 11-14 of the office action mailed on 02/14/2008.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 17 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

For clarity and completeness of this office action, the reasons of record advanced on pages 11-14 of the office action mailed on 02/14/2008 is reiterated below with modifications addressing claim amendments.

Roizman et al. teaches the following: **(i)** Novel modified HSV vectors for gene therapy (See abstract, Roizman et al., 2001), which reads on the limitation "an expressible non-herpes simplex virus nucleotide sequence encoding a desired protein" recited in claim 16 of instant applicant application, **(ii)** The function of the gene γ34.5 in its ability to enable the virus to replicate, multiply and spread in the central nervous system (CNS) was demonstrated by a set of recombinant viruses and by testing their abilities to cause fatal encephalitis in the mouse brain. The mutant viruses lacking the gene therefore lost their ability to multiply and spread in the

CNS and eyes and therefore are non-pathogenic. See Chou et al., Science, 250: 1212-1266, 1990 (See lines 35-42, col. 4, Roizman et al., 2001), **(iii)** The use of the HSV-1 virus with a null mutation in the γ34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the CNS and in all other parts of the body. The "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread. Therefore, given the ability to target tumors within the CNS, the γ34.5 minus virus has proven a powerful therapeutic agent for hitherto virtually untreatable forms of CNS cancer (See bridging paragraph, col. 5-6, Roizman et al., 2001). Roizman et al. further teaches that the γ34.5 gene placed under a suitable target specific promoter in the context of treating a tumor cell (which reads on the limitation of claim 28 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001), and **(iv)** The embodiment of the present invention describes a method which involves combining ICP34.5 (i.e. γ34.5) or a biological functional equivalent thereof with a pharmaceutically acceptable carrier in order to form a pharmaceutical composition, which reads on claim 29 of instant application.

Roizman et al., do not teach do not teach a herpes simplex virus with a genome that expresses an exogenous cytokine gene recited in claim 16.

Vile et al. teaches that (i) transduction of tumor cells *in vitro* with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned *in vivo* to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994), and (ii) constitutively producing cytokines such as IL-2, IL-4, and GM-CSF could be

use as "cancer vaccine" by activation of immune system (See conclusions, right column, second paragraph, Vile et al., 1994), and that (iii) use of the 5' flanking region of the murine tyrosinase gene directs expression of three different cytokine genes murine interleukin 2 (IL-2), IL-4 and macrophage colony-stimulating factor (M-CSF) specifically to murine melanoma cells (See abstract, Vile et al. *Ann Oncol.* 5 Suppl 4:59-65, 1994).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Roizman et al. (2001) regarding the characteristics of a mutant herpes simplex virus comprising a disrupted γ34.5 herpes simplex, which is non-pathogenic and has lost the ability of to multiply and spread in the CNS and in all other parts of the body, with the teachings of Vile et al. (1994) regarding exogenous expression of a cytokine gene results in diminishment or elimination of tumorigenicity of tumor cells via elicitation of immune response to arrive at the claimed HSV with disrupted both γ34.5 that exhibits no neurovirulence, and expressing a cytokine gene that elicit an immune response against a tumor cell, as recited in claims 16, 18-20, and 28-32 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. with the teachings of Vile et al. (1994) because the γ34.5 gene mutation would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), and the exogenous expression of a cytokine gene would result in diminishing or eliminating tumorigenicity of tumor cells, as taught by Vile et al.

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above. Applicant argues that the combination of Roizman et al. and Vile et al. is based on "obvious to try" rational that is improper under the statute and governing case law. In this regard, Applicant cites the U.S. Supreme Court's decision, KSR International Co. v. Teleflex Inc., and EXAMINATION GUIDELINES FOR DETERMINING OBVIOUSNESS UNDER 35 U.S.C. § 103..., published in the Federal Registrar, Vol. 72, No. 195 (October 10, 2007) as support. Applicant argues that the Examiner has failed to meet the initial burden, pursuant to the Guideline requirements, of establishing a *prima facie* case of obviousness because, contrary to the Examiner's contention, there was no reasonable expectation of success in view of the state of art at the time

of filing. Applicant argues that the contemporaneous art was hardly one characterized by "a finite number of identified, predictable potential solutions to the recognized ... problem," namely, the treatment of malignant tumors, and to the contrary, the skilled artisan would have encountered panoply of co-treatments that might be combinable with oncolytic HSV. Applicant argues that as the accompanying Rule 132 declaration of inventor Samuel Rabkin demonstrates, moreover, the prior art was replete with publications evidencing a contemporaneous understanding in the field that cytokines, such as IL-1α, IL-2, IL-3, TNF, INF-α, IFN-β, INF-γ, M-CSF-1 and GM-CSF, ***protect*** a host from HSV infection and ***diminish*** replication of HSV in the host cells. Applicant indicates that as Dr. Rabkin attests, this conventional wisdom of the day would have led the skilled artisan away from expressing cytokines in the replication competent HSV for purposes of tumor therapy, as presently claimed, since therapy with such mutant HSV requires HSV to infect and replicate in tumor cells of the host, in order to kill tumor cells. Applicant indicates that further alteration of such mutant HSV to express cytokines is done to elicit an immune response against the tumor cell, enhanced by cell killing due to the HSV infection. Id. at page 6, paragraph [0077]. Applicant argues that, the skilled artisan would have expected that expression of a cytokine to protect the cells from HSV infection and replication, which would diminish the therapeutic effect of the claimed, replication-competent HSV, and by the same token, the skilled artisan would not have expected, as the Examiner

contends, that combining cytokines with the mutant HSV might result in an enhanced tumor therapy.

Responses to Applicant's Arguments

With regard to the scientific aspect of Applicant's arguments that cytokines, such as IL-1α, IL-2, IL-3, TNF, INF-α, IFN-β, INF-γ, M-CSF-1 and GM-CSF, protect a host from HSV infection and diminish replication of HSV in the host cells, the Examiner agrees in general with the declaration by Dr. Rabkin, and the references cited therein, with regard to the biological functions of a cytokine in protecting a host from herpes simplex virus (HSV) infection and in preventing HSV replication in the host. It is noted that Applicant's arguments are applicable as to endogenous expression of cytokine (i.e. pre-existing cytokine before virulent HSV infection) as part of immune system that can prevent virulent HSV infection. Nevertheless, the claims are directed to expressing a cytokine gene from a mutated HSV vector which is non-neurovirulent and replicates primarily, if not exclusively, in fast dividing tumor cells. In this setting, the cytokine gene is incorporated into the mutated HSV genome and will be expressed only after claimed mutated HSV vector infect targeted tumor cells. Therefore, Applicant's arguments pertaining to the general immune protective effect of cytokine expression in preventing virulent HSV infection have been fully considered and found not persuasive. Furthermore, Vile et al. clearly states that transduction of tumor cells with cDNA encoding various

cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity of tumor cells (See first sentence of Introduction, page S59, Vile et al., 1994).

With regard to the legal aspect of Applicant's arguments that "obvious to try" rational that is improper under the statute and governing case law because the skilled artisan would have encountered panoply of co-treatments (which Applicant asserts it's not a finite number) that might be combinable with oncolytic HSV, the Examiner notes that, as cited above, Vile et al. clearly states that transduction of tumor cells with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity of tumor cells (See first sentence of Introduction, page S59, Vile et al., 1994) and constitutively producing cytokines such as IL-2, IL-4, and GM-CSF could be use as "cancer vaccine" by activation of immune system (See conclusions, right column, second paragraph, Vile et al., 1994). The teachings by Vile et al. provide strong motivation for a skilled artisan to combine the anti-tumor effect of cytokine taught by Vile et al. to be expressed from the non-pathogenic HSV vector by the teachings of Roizman et al. Therefore, Applicant's arguments regarding the assertion that combining the teachings of Roizman et al. and Vile et al. being based on an "obvious to try" rational with infinite number to be identified, have been fully considered and found not persuasive.

5. Claims 16, and 18-19 **remain** rejected and amended claim 20 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) taken with Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994) as applied to claims 16, 28, and 29 above, and further in view of Chang et al. (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991). Applicant's arguments filed 05/14/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-17 of the office action mailed on 02/14/2008. The inclusion of claim 20 in this rejection is necessitated by claim amendments filed on 05/14/2008.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 17 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any.

For clarity and completeness of this office action, the reasons of record advanced on pages 14-17 of the office action mailed on 02/14/2008 is reiterated below with modifications addressing claim amendments.

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 taken with Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that comprises alteration in the ribonucleotide reductase (RR) gene (recited in claim 19 of instant application).

At the time of filing of instant application, a herpes simplex virus with a genome that is altered in the ribonucleotide reductase gene was known in the art. For instance, Chang et al. teaches that herpes simplex virus type-1 (HSV-1) is able to infect both non-neuronal and neuronal cells (See introduction, Chang et al., 1991). Chang et al. also teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) is a useful vector for gene delivery into neuronal cells. Chang et al. used hrR3, a genetically engineered HSV-1 mutant which has an in-frame insertion of the bacterial lacZ gene into the HSV gene that encodes the large subunit (ICP6) of ribonucleotide reductase (RR), resulting in the ICP6::lacZ chimeric gene. Chang et al reported that the infection was performed in the presence of acyclovir, hrR3 appeared to become "latent". Chang et al. further teaches that the introduction of a foreign gene into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991). Chang et al further teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine (i) the characteristics of a mutant herpes simplex virus comprising an nucleotide sequence encoding a cytokine, a disrupted γ34.5 herpes simplex, which is non-pathogenic and has lost the ability of to multiply and spread in the CNS and in all other parts of the body, as taught by combined teachings of Roizman et al. 2001 and Vile et al., 1994, with (ii) the characteristics of a RR-negative herpes simplex virus that can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, as taught by Chang et al. 1991.

It would have been obvious at the time of filing to combine the teachings of Roizman et al. 2001, and Vile et al., 1994, with the teachings of Chang et al. 1991, to arrive at the claimed herpes simplex viruses as recited in claims 16 and 18-20 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. 2001, Vile et al., 1994, with the teachings of Chang et al. 1991 because the disrupted γ34.5 gene renders the HSV vector non-pathogenic and the disrupted ribonucleotide reductase gene render the HSV vector specific targeting to fast dividing tumor cells without harming healthy cells, for the treatment of CNS or non-CNS cancers. Combination of the mutations would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), that targets specifically fast dividing tumor cells, as taught by Chang et

al., 1991, which indicates the disruption of ICP6, either by LacZ insertion in the ICP6:LacZ strain or by deletion in the ICP6Δ strain, results in severe growth impairment in non-dividing cells (See first paragraph, left column, page 438).

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994, and (3) the demonstration that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) vector for introduction of a foreign gene can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, by the teachings of Chang et al., 1991.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments and ***Responses to Applicant's Arguments*** are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al.

6. Claim 30-32 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) taken with Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994) as applied to claim 16, 17, 28, and 29 above, and further in view of McKay et al. (WO 92/14821, publication date 09/03/1992, PCT/US92/01375, priority date 02/22/1991), and Wright, Jr. (US 5,639,656, issued Jun. 17, 1997, filed 03/31/1994). Applicant's arguments filed 05/14/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 17-20 of the office action mailed on 02/14/2008.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 17 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any.

For clarity and completeness of this office action, the reasons of record advanced on pages 17-20 of the office action mailed on 02/14/2008 is reiterated below with modifications addressing claim amendments.

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 taken with Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that expresses a exogenous cytokine gene, wherein an essential viral gene product of said virus is under the control of a tumor cell-specific promoter rather than its own promoter, wherein said promoter being nestin promoter, basic fibroblast growth factor (bFGF) promoter, or epidermal growth factor (EGF) promoter, as recited in claims 30-32 of instant application.

At the time of filing of instant application, it was known in the art that the expression of certain growth factor genes including bFGF, EGF, nestin genes can serve as markers for detection of various cancers, indicating the promoters of these growth factors being tumor specific with respect to its regulation. For instance, McKay et al. teaches that nestin expression as an indicator of neuroepithelial brain tumors, indicating the nestin promoter being tumor specific with respect to its regulation (See title and abstract, WO 92/14821, publication date 09/03/1992). Wright, Jr. 1997 teaches the expression of bFGF, EGF can be used as biological markers of prostate cancer (CaP) or benign prostate hyperplasia (BPH) (See title and lines 30-36. column 2, Wright et al., 1997). Furthermore, as indicated before, Roizman et al. further teaches that the □34.5 gene placed under a suitable target specific promoter in the context of treating a tumor cell (which reads on claim 28 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001). Accordingly, it would have been *prima facie*

obvious the nestin promoter, bFGF promoter, EGF promoter are tumor cell specific promoters, and thereby can be used for expressing an essential viral gene as recited in claims 30-32 of instant application by the combined teachings of Roizman et al., 2001, McKay et al., 1991, and Wright, 1997.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to exogenously express a nucleotide sequences encoding a cytokine, whose transduction of tumor cells with cDNAs encoding various cytokines has been shown to diminish or eliminate tumorigenicity in syngeneic animals, in a γ34.5 defective HSV vector, as taught by the combined teachings of Roizman et al., 2001 and Vile et al., 1994, and to have an essential viral gene product under the control of a tumor cell-specific promoter of nestin or bFGF, or EGF, as taught by the teachings of Wright or McKay et al., in the said herpes simplex virus vector with disrupted both γ34.5 and expressing nucleotide sequences encoding a cytokine, to ensure that the said HSV vector exhibits no neurovirulence and specifically infecting the fast dividing cancer cells in the cancer cells, by the combined teachings of Roizman et al., 2001, Vile 1994, and Chang et al., 1991.

It would have been obvious at the time of filing to combine (i) the teachings of Roizman et al. 2001, and Vile et al., 1994, regarding a HSV vector for cancer treatment with the expression of a nucleotide sequences encoding a cytokine from a HSV vector, wherein as essential viral gene product placed under a suitable target

specific promoter, with (ii) the teachings by Wright or McKay et al., regarding gene product being under the control of the tumor specific promoters of nestin or bFGF, or EGF to arrive at the claimed herpes simplex viruses as recited in claims 30-32 of instant application.

One having ordinary skill in the art would have been motivated to utilize the HSV vector that exhibits characteristics favorable gene transfer, expresses nucleotide sequence encoding a cytokine, and infects specifically to tumor cells, by combined teachings of Roizman 2001, Vile et al., 1994, and Chang 1999, to introduce the expression of a nucleotide sequences encoding a cytokine for gene therapy, and said HSV vector comprises an essential gene product under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., becasue the HSV vector being non-pathogenic and specifically infect tumor cells without harming healthy cells, and the exogenous nucleotide sequence encoding cytokine is expressed only in the tumor cells, as an essential viral gene product is expressed in a tumor specific manner.

There would have been a reasonable expectation of success given (1) the characteristics of an HSV vector by the combined teachings of Roizman et al. and Chang et al. being non-pathogenic and specifically targeting to fast dividing tumor cells, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of

Vile et al., 1994, (3) the demonstration of nextin expression in a brain tumor specific manner by the teachings of McKay et al, and the expression of bFGF and EGF in a prostate cancer specific manner by the teachings of Wright.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments and ***Responses to Applicant's Arguments*** are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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